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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/805,804	03/22/2004	David C. Baulcombe	101044.53943D2	9959

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EXAMINER	
MEHTA, ASHWIN D	

ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 10/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/805,804	**Applicant(s)** BAULCOMBE ET AL.	
	Examiner Ashwin Mehta	**Art Unit** 1638	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 26 September 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *4* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☒ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *33-36,40,41,60-80,83,93-107 and 109-115*.
   Claim(s) withdrawn from consideration: *45-59,81,82,84-92 and 108*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☒ Other: See Continuation Sheet.

ASHWIN D. MEHTA, PH.D.
PRIMARY EXAMINER

Continuation of 5. Applicant's reply has overcome the following rejection(s): if it were entered, the claim amendments would have overcome the following: under 35 U.S.C. 112, 2nd paragraph, the rejection of claims 33 and 40 over the recitation, "silencing agent"; the rejection of claim 35, in light of its cancellation; the rejection of claim 33 for "the targeted region"; the rejection of claim 75 for "said organism"; the rejection of claim 76 under 35 U.S.C. 112, 1st paragraph, lack of enablement; the rejection of claim 97, for the recitation, "said cell"; the rejections under 35 U.S.C. 102 (b) and (e).

Continuation of 11. does NOT place the application in condition for allowance because: Applicants response does not overcome the objection to the specificaiton for containing new matter. Applicants argue that the language in the specification at page 2, lines 14-20, 21-26, and 22-33 teaches that the sense and antisense molecules are complementary to each other, and use of language in the abstract directed to "complementary short RNA molecules" which could hybridize with a target RNA has ipsisimus verbis support in the specification (response, pages 19-21). However, support is not found for "corresponding complementary short sense RNA molecules". The specification as filed does not describe that SARMs and SSRMs are complementary to one another.

Applicants' reply does not overcome the rejection of claims 33, 40, 60, 77, 93, 100, 102, and 109, and claims dependent thereon under 35 U.S.C. 112, 2nd paragraph. Applicants argue that in light of the definition of SRMs provided on page 2, lines 28-33 of the specification, the claim amendments clarify that SRMs consist of SARMs and SSRMs (response, page 24). However, "short complementary RNA molecules (SRM)" appears to indicate a SRM is a double stranded molecule made of up a SARM and a SSRM that is complementary to it, whereas the recitation on page 2 pointed out by Applicants indicats the complementarity of a SRM to a target RNA. Applicants argue that whether the 25 nt effector is double stranded or not in this context is purely semantic, that the specification provides evidence that in silencing, SARMs and corresponding SSRMs are detected, that in the cellular milieu they would hybridize with each other and form short double-stranded molecules when not incorporated into the PTGS machinery of the organsim. Applicants point to page 9, line 30 for support for "PTGS machinery of the organism" (response, paragraph bridging pages 25-26). However, regardless of how a method works or what is happening during PTGS, the meanings of all terms in a claim, everything that is encompassed by any term in a claim, must be clearly understood. This cannot be waved off as a matter of "semantics". Further, the paragraph on page 9 in which "PTGS machinery of the organism" appears does not indicate that SRMs are double stranded, but rather discusses a method of finding a suitable site on an mRNA to target for silencing using an antisense construct. On page 27, Applicants argue that the specification as originally filed discloses three classes of molecules, SARMs, SSRMs, and SRMs which comprise SARMs and SSRMs. However, the specification discloses two classes of molecules, SARMs and SSRMs, and collectively refers to both of them as SRMs. The word "collectively" does not mean that a SRM is a double stranded moleclue. Applicants also argue on page 27 that an inventor need not know exactly how his invention works, and then continues on pages 27-29 to discuss post-filing advancements in the understanding of PTGS. However, this is not an enablement rejection and Applicants are not being asked here to know exactly how the invention is working. Applcants point to original claims 1, 5, 6, and 26 and argue that they encompass three classes of molecules, SRMs, SARMs, and SSRMs, and claims 1-3 of US Patent No. 6753139, which issued from a parent application, and argue that it supporst SRMs as encompassing SARMs and SSRMs (pages 28-31). However, while the original claims and '139 support a SRM being either a SSRM or a SARM, they do not indicate that a SRM can be a double stranded molecule.

Applicants' reply does not overcome the rejeciotn of claims 33, 40, 60, and 93 under 35 U.S.C.. 112, 2nd paragraph. Applicants argue that no less than 120 U.S. patents have issued whrein the term "corresponding" is utilized to refer to relationships between nucleic acid molecules. Applicants argue that one skilled in the art would readily appreciate that the phrase "corresponding' sense molecules refers to those molecules which could hybridize to antisense molecules of the same target (response, pages 33-35). However, the patentability determination of an application is made based on the disclosure of that application, not on other applications or patents. The Examiner maintains that the term is indefinite for the reasons of record.

Claims 33-36 and 111 remain rejected under 35 U.S.C. 112, 1st paragraph, lack of enablement. Applicants argue that an inventor need not appreciate the molecular mechanism underlying his invention, that it is not required that the SRMs base pair with genomic DNA or any other molecule while the SRMs are in a duplex form, and that there is no mention of genomic DNA in the claims (pages 37-38). First, Applicants' discussion itself about the PTGS pathway indicates that SARMs and SSRMs base pair with RNA, not genomic DNA. Further, claim 33, for example, in the claims version filed March 17, 2006, lines 3-5, stated that the silencing agent base pairs with said target gene. A gene is genomic DNA, and that claim version did require base pairing with a gene. In the response filed October 2, 2006, claim 33, while indicating first that the short complementary RNA molecules could base pair with target RNA encoded by said target gene, it then indicates that SARMs and SSRMs could base pair with "the target". The claim is unclear in that it does not indicate if "the target" is referring to the target RNA or target gene. The rejection would still apply if the recitation is referring to target gene. Claims 60 and 93 and claims dependent thereon would be added to the rejection, because they recite that the SARM and SSRM could base pair with sense or antisense strands, respecitively, of a gene. While "could" base pair does not indicate that the base pairing is required, the base pairing of the SARM and SSRM with a strand of the target gene is encompassed. Applicants request that the reasoning for including claim 111 in the rejection in the last Office action be provided, because the claim was not included in the rejection in the first Office action. Applicants presume that it was included because it depends from claim 33 (page 39). Applicants' presumption is correct. This issue of the enablement rejection was first raised in the Office action mailed May 26, 2006 and it was necessitated by the amendment to claim 33, so the finality of the last Office action was proper.

Applicants reply does not overcome the rejection of claims 33-36, 40, 41, 60-80, 83, 93-107, and 109-115 under 35 U.S.C. 112, 1st paragraph. Applicants argue, in response to a statement in the last Office action that "collectively is not synonymous with complementary'", that the specification states the nature of the SRMs on page 2, lines 30-32, i.e. short complementary molecules which could base pair with the target RNAs (response, page 40). However, this passage on page 2 is referring to the complementarity with a target RNA, not of SRMs to one another. Further, page 2 does not state that the abbreviation "SRM" stands for "short complementary RNA molecule. Rather, the specification at page 4 states, "The term 'SRMs' is used to describe the short RNA molecules". Applicants argue that the claims have been amended to remove the combination of "corresponding" and "complementary" (page 40). However, the recitation, "short complementary RNA molecules (SRM)" implies that the term enocmpasses a double-stranded molecule, which is not contemplated by the specificaiton as originally filed. Applicants argue on page 41 that the Examiner seems to be seeking to put words into the specification. However, the previous Office action, rather clearly, made no such indication. Applicants on page 41 also indicate that they are unclear what the Examiner meant by "individual short RNA molecule", recited in the last Office aciton, and indicate that the

specification does not require that the SARM and SSRM be part of the same linear chain of nucleotides forming a single "individual short RNA molecule", although they believe this is not excluded. However, it is rather clear that by "individual short RNA molecule" the Examiner was merely making reference to one short RNA molecule, and was being used in the rejection to explain why a SRM was not contemplated in the specification as being a double-stranded molecule. The Examiner, again rather clearly, was not making reference toa linear chain. Applicants point to a statement from the Office action mailed October 21, 2005 and assert that it indicates the Examiner acknowledged that the specificatioin enables methods using double stranded SRMs (response, pages 41-42). That this statement appeared in that Office action is clear. However, this is not an enablement rejection, but rather a written description rejection. The issue here is not enablement, but rather new matter and what was contemplated in the application as originally filed. In response to the discussion in the rejection in which the Examiner pointed to pages 11-12 of the specificaiton, Applicants argue that the disclosure implies that when SARMs are detected, corresponding complementary SSRMs are detected in the same amount, that the common effector of PTGS are the SRMs, that SARMs and corresponding complementary SSRMs are encompassed within the definition of SRMs (pages 42-43). That the specification describes a SRM as being a SARM or a SSRM is not disputed. However, for the reasons of record, it is maintained that the specification does not provide written descriptive support for a SRM as being a double stranded molecule.

Regarding the rejection of claims 75 and 97 under 35 U.S.C., 112, 1st paragraph, lack of written description, Applicants direct attention to page 25 of the specification which indicates that 25 nt RNA species was isolated following PVX infection of untransformed N. benthamiana leaves, and the virus thus infected these cells and its expresion was silenced (response, page 44). However, the claims are not limited to a target gene expressed by a virus within a plant cell, but also parasites and predators within a plant cell, which does not have support in the specifcation.

The claims are being examined according to the elected host of plant cells and plants. However, it is pointed out that the amendment to claim 70 encompases a method in which a transgenic human is made, which is non-statutory. Claim 70 depends ultimately with claim 60 which is drawn to a method in which RNA molecules are introduced into a cell. Claim 67 limits the introduction of the RNA to being from a DNA vector or construct that is stably maintained by said cell, which indicates that it is within genomic DNA. This embodiment is also encompassed by claim 60, as claim 67 depends from it, and this embodiment is not excluded by claim 70, the amendment of which recites that the cell can be in a human organism.

Continuation of 13. Other: the reply filed 26 September 2006 is a supplemental amendment submitted after Final rejection. Applicants filed an intital amendment after Final rejection on 28 August 2006, which was not considered, given the filing of the supplemental amendment .